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Irritable bowel syndrome immune hypothesis. Part two: the role of cytokines

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ABSTRACT

Objective: To review the available evidence on the role of interleukins in the etiopathogenesis of Irritable Bowel Syndrome.

Methods: Bibliographic retrieval on PubMed including the MeSH terms "Irritable Bowel Syndrome, "Immune System", "Cytokines" and "Interleukins".

Results: Sixteen case-control studies and one randomised controlled trial were retrieved. The blood appears to have a high concentration of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8) and lower concentration of IL-10, an anti-inflammatory cytokine, even though the findings are disparate and heterogeneous. As many as 33 genes were found, each with different expressions, and a diminished expression of cytokines in the colon mucosa of patients with IBS, which have not been previously described in any other pathology.

Conclusions: In patients with IBS, a clear profile of cytokine levels in the blood does not appear to exist, although an imbalance between them can be observed. Moreover, there are indications that give reason to believe that the different subsets of patients with IBS could present cytokine profiles in different blood. On the other hand, in the intestine, high cytokine secretion levels are not detected, contrary to what would be expected. Further studies are required to substantiate these findings.

Key words: Irritable bowel síndrome. Immune system. Cytokines. Interleukins. Psychoneuroimmunology. Systematic review.

RESUMEN

Objetivo: Revisar la evidencia disponible sobre el papel de las interleukinas en la etiopatogenia del Síndrome del Intestino Irritable.

Métodos: Recuperación bibliográfica en PubMed, incluyendo los términos MeSH *"Irritable Bowel Syndrome, "Immune System", "Cytokines"* e *"Interleukins".*

Resultados: Se recuperaron 16 estudios casos-control y un ensayo clínico aleatorizado. A nivel sanguíneo, parece existir una concentración elevada de citokinas proinflamatorias (FNT-α, IL-1β, IL-6, IL-8) y disminuida de la IL-10, una citokina antiinflamatoria, si bien los resultados son dispares y heterogéneos. Se han encontrado hasta 33 genes, cada uno con una expresión diferente, y una expresión disminuida de citokinas en la mucosa del colon de pacientes con SII, que no se ha descrito hasta el momento para ninguna otra patología.

Conclusiones: En los pacientes con SII, no parece existir un perfil claro de los niveles de citokinas en sangre, si bien, si parece existir un desequilibrio entre ellas. Asimismo, hay indicios que hacen pensar que los distintos subgrupos de pacientes con SII podrían presentar un perfil de citokinas en sangre diferente. Por otro lado, a nivel intestinal, no se detectan niveles elevados de secreción de citokinas, en contra de lo que cabría esperar. Son necesarios más estudios para confirmar estos hallazgos.

Palabras clave: Síndrome del Intestino Irritable. Sistema inmune. Citokinas. Interleukinas. Psiconeuroinmunología. Revisión sistemática.

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INTRODUCTION

We present the continuation of an Evidence-Based Systematic Review on the Irritable Bowel Syndrome (IBS) Immune Hypothesis undertaken by our team (1), the Functional Digestive Disorders and Psychoimmunology Research Group within the framework of the Biomedical Research Map of the Aragon Institute of Health Sciences.

In part one, we reviewed the role of T-lymphocytes and mast cells in the etiopathogenesis of IBS. In this second part, we address the role of cytokines, immune mediators, in said functional digestive disorder.

This global review draws us closer to determining the role of the immune system in the etiopathogenesis of IBS.

METHODS

The bibliographic search was undertaken on the PubMed database (www.pubmed.gov) in December 2009. In the research strategy the MeSH terms "Irritable Bowel Syndrome, "Immune System", "Cytokines" and "Interleukins" were employed in line with the methodology used in the first part of this Systematic Review (SR) (1). The methodological quality of the articles was assessed according to the recommendations of the Cochrane Collaboration (2,3).

In the SR, studies which fulfilled the following criteria and confines were included: the study of a set of patients with IBS in association with a control group (CG) and/or other pathologies; reference made to the etiopathogenesis of IBS from the standpoint of a probable immune hypothesis; studies undertaken on humans and articles published in Spanish or English. Excluded were those articles in which no relationship was found with said probable hypothesis and those conducted on animals. In order to analyze the findings it was considered whether the determination of the immune components, in this case the cytokines, was conducted by means of a blood test and/or biopsy (and the area in which it was performed), and, in addition, whenever possible, it was analyzed whether there were differences between the different subtypes of IBS (diarrhoea [D], constipation [C], alternating [A]), or between the form of onset of the disorder (post-infectious [PI], non-PI).

RESULTS

A total of 17 valid articles related to the IBS immune hypothesis were retrieved. One of them constitutes a randomized controlled trial (4) and the remaining 16 are case-control studies (5-20). The controlled trial has great methodological validity, although it does not refer to the sample representativeness (4).

Throughout all the publications, the patient immune profile had been examined by means of performing a blood test (4,6,8,10,11,13-15,17-20) and/or a biopsy of one or more parts of the intestine (5,7,9,12,16,18,20).

With the exception of two studies (5,6), the IBS diagnosis was made according to Rome I Criteria (7,8) or Rome II Criteria (4,9-20). The researchers followed different criteria when studying patients with IBS. Some studies selected all the patients with IBS without taking IBS subtypes characteristic thereof into account (6,8,10,19). Others differentiated between patients with PI-IBS and patients with non-PI-IBS (7,9,12,15). Finally, others differentiated between patients according to the predominance of symptoms: D-IBS, C-IBS, A-IBS (5,11-18,20).

Despite differentiating between these three subtypes, the majority of the studies did not have a sufficient sample size so as to establish significant differences in the immune profile between the subsets. One study exclusively selected patients with PI-IBS (7) and another two studies chose patients with D-IBS (5,14). The main characteristics of the articles retrieved are outlined in table 1.

Cytokines

Cytokines are proteins produced by leukocytes although they may also be secreted by other cells such as glial cells. Fundamentally, they mediate innate and adaptive immune responses.

Chemokines are low molecular weight cytokines that attract leukocytes to the foci of infection and/or inflammation.

With regard to their role in inflammation, pro-inflammatory cytokines (IL-1α, IL-1β, IL-2, IL-6, IL-12, IL-18, TNF-α, IFN-γ) and anti-inflammatory cytokines (IL-4, IL-10) (21-23) are described.

The chronic and persistent activation of helper T-lymphocytes gives rise to their differentiation into Th1 lymphocytes or Th2 lymphocytes. There are no phenotypic markers that identify these cells, which therefore call for their in vivo culture and cytokine analysis in order to differentiate between both subsets. Th1 lymphocytes primarily secrete interferon γ (IFN- γ), interleukin 2 (IL-2) and the tumour necrosis factor β (TNF-β). Conversely, Th2 lymphocytes mainly secrete IL-4, IL-5, IL-6, IL-10 and IL-13.

The differentiation of Th0 lymphocytes from Th1 lymphocytes is induced, essentially, by IL-2 and IFN-γ that, in turn, inhibit the differentiation of Th2 lymphocytes. Similarly, the differentiation of Th0 lymphocytes from Th2 lymphocytes is induced by IL-4, which together with IL-10, inhibit the differentiation of Th1 lymphocytes.

The Th1 response promotes cellular immunity by means of stimulating CD8+ T-lymphocytes, NK cells and macrophages, as well as nitric oxide and other inflammatory mediators that drive chronic delayed-type inflammatory responses. The Th2 response promotes humoral immunity by means of stimulating eosinophils, mast cells and B lymphocytes (24,25).

Cytokines in the blood

A low frequency of -1082*G allele has been observed in patients with IBS, responsible for coding a high production of IL-10, although this difference was not signifi-

Table I. Characteristics of the studies retrieved

Study, year (reference)	*Diagnostic criteria and IBS type Participants: number, gender, age*		*Intervention and outcome assessment*
Khan, 1994 (5)	D-IBS: 10	CG: 10	Colon biopsy 50 cm from the anus. IL-1β, IL-1RtI (IL-1β type I receptor), α-1 sodium pump isozyme, SP, and SP (NK-1) receptor mRNA.
Motzer, 2002 (6)	Rome Criteria IBS: 12 (F: 12, MA: 32 SD 8.8)	CG: 12 (F: 12, MA: 32 SD 8.8)	Blood test from day 5 to 7 following the start of menstruation, urine test. Sense of coherence questionnaire, BDQ, SCL-90-R, Global Severity Index. NK cell cytotoxicity and percentage, percentage of NK / T cells, in vitro IFN-γ production, Serum cortisol, estradiol and progesterone, urine adrenaline and noradrenaline.
Gwee, 2003 (7)	Rome I Criteria PI-IBS: 8 (F: 4, MA: 44 SD6.8)	IFN-CG: 7 (F: 4, MA: 48 SD5.2) CG: 18 (F: 14, MA: 30 SD2.4)	Rectal biopsy performed during the acute phase of gastroenteritis and three months after. IL-1β and IL-1ra (IL-1β receptor antagonist) mRNA.
Gonsalkorale, 2003 (8)	Rome I Criteria *IL-10 genotype:* *TGF-β1 genotype:* IBS: 134	Rome I Criteria *IL-10 genotype:* *TGF-β1 genotype:* CG: 127	Blood test. DIL-10 (-1082 position) and TGF-β1 (codon 10, +869 position, codon 25, +915 position) allele distribution and genotype.
Wang, 2004 (9)	Rome II Criteria IBS: 56 (F: 31, MA: 43.3); PI-IBS: 27, Non-PI-IBS: 29	CG: 12 (F: 7, MA: 43.4)	Biopsy of the terminal ileum and rectosigmoid junction mucosa. mRNA expression of IL-1α, IL-1β and IL-1ra (receptor antagonist). MC, nerve fibres: NSE (Neuron-Specific Enolase), SP, 5-HT (Serotonin or 5-hydroxytryptamine), CGRP (Calcitonin Gene-Related Peptide).
Elsenbruch, 2004 (10)	Rome Criteria IBS: 14 (F: 14, MA: 47.7 SD3.6)	CG: 14 (F: 14, MA: 40.0 SD2.6)	Fasting patients ingested 500 ml of Fresubin (a chocolate-flavoured, standardised liquid nutrition solution containing a total of 500 Kcal) within a 10-minute time frame. The baseline data were collected and, subsequent to the ingestion of Fresubin, 4 postprandial periods were completed, the first had a 15-minute duration and the remaining periods had a 30-minute duration. Blood samples were taken following each period. CD3+, CD3+CD4+ and CD3+CD8+ lymphocytes, NK cells (CD3-CD16+CD56+ lymphocytes), B cells (CD3-CD20+ lymphocytes), monocytes (CD14+ leukocytes), granulocytes, TNF-α and IL-6 production in vitro, norepinephrine, cortisol, prolactin. Blood pressure, heart rate. Gastrointestinal Symptoms Questionnaire, State-Trait Anxiety Inventory, SCL-90-R.
van der Veek, 2005 (11)	Rome II Criteria IBS: 111 (F: 84, MA: 48.6 SD12.9); D-IBS: 35, C-IBS: 27, A-IBS: 34, unknown subtype: 15	CG: 162 (F: 98, MA: 37.6 SD15.6)	Blood test. TNF-α (-308 position) and IL-10 (-1082 and -819 positions) allele distribution and genotype.
O'Mahony, 2005 (4)	Rome II Criteria Treatment group: LG, BG, PG: 75 (F: 64%, MA: 44.3) D-IBS: 28%, C-IBS: 26%, A-IBS: 45%	CG: 20 healthy patients	Clinical trial: Patients were instructed not to take any medication – 4 weeks prior to the beginning of the probiotic intake – that could influence the intestinal motility or the absorptive function, including laxatives and antidiarrheal agents, as well as any preparation that could alter the enteric flora, including antibiotics and commercially available probiotic preparations. Malted milk probiotics were added depending on the group. Patients had to take a once-daily dose in the morning for eight weeks with four weeks of follow-up. Blood test and stool analysis. Symptoms, faeces characteristics, abdominal pain or discomfort, bloating or distention, bowel movement difficulty: difficulty or urgency with evacuation, bowel movement frequency: number of faeces per day, stool consistency: Bristol Stool Scale. Irritable Bowel Syndrome Quality of Life questionnaire. IL-10, IL-12.
Öhman, 2005 (12)	Rome II Criteria IBS: 33 (F: 19, MA: 42 SD12); D-IBS: 20 (4 with PI-IBS), C-IBS: 4 (1 with PI-IBS), A-IBS: 9	UC: 23 (F: 10, MA: 42 SD11). Patients with UCr y UCa. CG: 15 (F: 7, MA: 53 SD8)	8 biopsies from the ascending and sigmoid colon, blood test. Ascending and sigmoid colon lamina propria lymphocytes. Peripheral blood lymphocytes. MAdCAM-1+ (mucosal addressin cell adhesion molecule–1), IFN-γ, CD4+, CD8+, Intβ7, CD45RA.
Dinan, 2006 (13)	Rome II Criteria IBS: 76 (F: 50, MA: 34.6 SD13.1); IBS: 36, C-IBS: 10, A-IBS: 30.	CG: 75 (F: 50, MA: 30.2 SD13.5)	Blood test. Group 1: cytokine levels. IBS: 49, CG: 48. IL-6, IL-8, IL-10, sIL-6R (IL-6 soluble receptor), TNF-α. Group 2: corticotropin-releasing hormone (CRH) stimulation test, plasma levels of ACTH and cortisol. IBS: 21, CG: 21. Group 3. Dexamethasone (1mg) challenge (glucocorticoid). IBS: 27, CG: 27. Gastrointestinal Symptom Rating Scale.
Lucas, 2007 (14)	Rome II Criteria D-IBS: 13 (F: 10, MA: 45 SD13.1)	IBDG: 10 (F: 6, MA: 48 SD13.4) RG: 10 (F: 9, MA: 42 SD6.4) CG: 15 (F: 12, MA: 36 SD7.9)	Blood test. Basal TNF-α and IL-10, β-adrenergic TNF-α and IL-10 modulation, TNF-α glucocorticoid modulation. BDQ.

(It continues in the following page)

Table I. Characteristics of the studies retrieved (cont.)

Study, year (reference)	*Diagnostic criteria and IBS type* *Participants: number, gender, age*			*Intervention and outcome assessment*
Liebregts, 2007 (15)	Rome II Criteria IBS: 55 (F: 33, MA: 39.5); D-IBS: 20 (5 with PI-IBS), C-IBS: 17, A-IBS: 18		CG: 36 (F: 23, MA: 37.5)	Blood test. BDQ, HADS. Basal and stimulated TNF-α, IL-1β and IL-6.
Macsharry, 2008 (16)	Rome II Criteria IBS: 59 (F: 59, MA: 36); D-IBS: 29%, C-IBS: 19%, A-IBS: 52%.		IBDG: 28 (F: 28, MA: 37) CG: 39 (F: 39, MA: 46)	7 biopsies from the sigmoid colon. Gene expression: to identify those genes with a different gene expression in the set of patients with IBS compared to the CG and IBDG. IBS: 9, CG: 8. Quantitative gene expression: IL-1β, IL-8, CCL-20, EGR1, CCL-5, SECTM1, IL-10, IL-12, FCT-β, CXCL-10, IL-6, FOXP-3. IBS : 22, CG: 21. Protein secretion: IL-8, CXCL-9, CCL-2, CXCL-10, IL-1β, TNF-α, IL-6.
Dinan, 2008 (17)	Rome II Criteria IBS: 37 (F: 24, MA: 18 - 53); D-IBS: 18, C-IBS: 5, A-IBS: 14.		DG: 14 (F: 10, MA: 58.8 SD7.9) CG: 37 (F: 24, MA: 56.5 SD9.5)	Group 1: Fasting patients took pyridostigmine 120 mg (acetylcholinesterase inhibitor) orally. Blood test at 0, 60, 90, 120 and 180 minutes. IBS: 21, CG: 21. Basal levels of GH, IL-6, IL-8, IL-10. Group 2: Subjects were tested on two occasions approximately 4 weeks apart. On one of the occasions fasting patients ingested pyridostigmine 120 mg orally. On the other occasion, blood was drawn 30 minutes after patients took procyclidine (antimuscarinic) 10 mg, and 30 minutes subsequent to the ingestion of pyridostigmine 120 mg. Blood was drawn at -30, 0, 60, 90, 120 and 180 minutes. IBS: 16, DG: 14, CG: 16. Monitoring of GH and IL-6. Symptom questionnaire.
Chang, 2009 (18)	Rome II Criteria *Study 1* IBS: 41 (F: 41, MA: 39.9 SD1.5); IBS: 15, C-IBS: 9, IBS-A: 17 *Study 2* IBS: 10 (F: 10, MA: 40 SD2.3); D-IBS: 10		*Study 1* CG: 25 (F: 25, MA: 33.0 SD2.1) *Study* 2 CG: 10 (F: 10, MA: 33.9 SD3.5)	*Study 1* Beginning at 9 am, blood samples for ACTH and cortisol were taken from fasting subjects every 10 minutes over a 24-hour period. Bowel symptom questionnaire, HADS, DSM-IV, gynaecological history, Stress Symptom Scale. *Study 2* Serial blood samples were taken at four time intervals: following a 30-minute rest period (baseline), immediately after and at 10 and 20 minutes after the sigmoidoscopy. Plasma ACTH, cortisol and catecholamine (adrenaline and noradrenaline) levels. 10 biopsies from the rectum and sigmoid colon. mRNA expression of: IL-1, IL-2, IL-6, IL-10, IL-12, IL-10/ IL-12, IFN-δ, TNF-α, RANTES. Bowel symptom questionnaire, HADS, DSM-IV, gynaecological history, Stress Symptom Scale
Kindt, 2009 (19)	Rome II Criteria IBS: 30 (F: 80%, MA: 37.0)		FD: 23 (F: 83%, MA: 39.0) NCCP: 15 (F: 73%, MA: 51.0) CG: 32 (F: 77%, MA: 30.5)	Blood test. Allergy screening: validated questionnaire and RAST: measurement of eosinophils and specific immunoglobulin E (IgE) antibodies. Measurement of cytokine production by lymphocytes: Peripheral blood mononuclear cells (PBMC): IL-5, IL-10, IL-13, IFN-γ; Monocytes: TNF-α, IL-10, IL-12; Serum: IL-6, IL-10. Immunophenotyping. Markers: CD3, CD5, CD4, CD8, ratio CD4/CD8, CD3+CD25+, CD3+HLADR+, D3+CD11b+, CD3+CD69+, CD3+CD28+, CD3+CD45RA+, CD3+CD45RO+, CD4+CD45RO+, CD4+CD45RA+, CD3+CD45RA+CD45R0+, CD3+CD16+CD56+, CD19, CD19+CD5+, CD3-CD16+CD56+.
Öhman, 2009 (20)	Rome II Criteria COHORT A: SII: 74 (M: 52, E: 34 DE16 SII-D: 26 SII-E: 11 SII-A: 37 GC: 30 (M: 20, E: 39 DE10)	COHORT B: SII: 26 (M: 23, E: 44 DE14) SII-D: 11 SII-E: 6 SII-A: 9 GC: 14 (M: 10, E: 33 DE9)	COHORT C: SII: 11 (M: 9, E: 33 DE9) SII-D: 4 SII-E: 1 SII-A: 6 GC: 10 (M: 7, E: 41 DE7)	COHORTS A and B: Blood test. COHORT C: Ascending and sigmoid colon biopsies. *Blood: Phenotype from T cells, CD4+ and CD8+ T cells, CD4+ CD69+ and CD8+* CD69+ T cells, CD4+Intβ7+HLA-DR+ and CD8+Intβ7+HLA-DR+ T cells, CD4+ CD25+ and CD8+ CD25+ T cells, CD4+ CD26L and CD8+ CD26L T cells, CD4+ and CD8+ T cells proliferation. Stimulated IL-2, IFN-γ, IL-10 and IL-1β secretion. Biopsy: CD4+ and CD8+ T cells proliferation, proliferation of lamina propria T-lymphocytes in the ascending and sigmoid colon. Questionnaire: IBS Severity Scoring System.

A: Alternating; ACTH: Adrenocorticotropic hormone; BDQ: Bowel Disease Questionnaire; BG: Bifidobacterium infantis group; C: Constipation; CG: Control group; D: Diarrhea; DG: Depression group; F: Females; FD: Functional dyspepsia; GH: Growth hormone; HADS: Hospital Anxiety and Depression Scale; IBDG: Inflammatory bowel disease group; IBS: Irritable Bowel Syndrome; IFN: Interferon; IFN-CG: patients who returned to normal bowel habits after acute gastroenteritis; IL: Interleukin; Intβ7: Integrin β7; LG: Lactobacillus salivarius group; MA: Mean age; MC: Mast cells; NCCP: Non-cardiac chest pain; PG: Placebo group; PI: Post-infectious; RG: Recent gastroenteritis; SCL-90-R: Symptom Checklist-90-Revised; SD: Standard deviation; SP: Substance P; TGF-β1: Transforming Growth Factor β1; TNF: Tumor necrosis factor; UC: Ulcerative colitis; UCa: UC active; UCr: UC in remission.

cant. On the other hand, in these patients, a high incidence of A allele positive subjects, both homozygous (-1082*A/A) and heterozygotes (-1082*G/A), has been observed which code a low and intermediate production of IL-10, respectively (8). Van der Veek et al (11), however, did not confirm this data, having observed regular levels of IL-10 genotypes and alleles at position -1082.

In patients with IBS, particularly in the D-IBS subset, a high incidence of patients with a TNF-α high-production genotype together with a IL-10 low-production genotype (11) has been described.

In regular subjects, following the ingestion of food, a decrease in TNF-α levels is observed which is not noted in patients with IBS, whereas IL-6 levels diminish in the same manner between the set of patients with IBS and the CG (10). Other authors have observed high basal levels of TNF-α, (15), IL-6 (13,15,17), IL-8 (13,17) and IL-1β (15) in patients with IBS, with D-IBS or with PI-IBS; or regular basal levels of TNF-α in patients with IBS (13) and with D-IBS (14), as well as regular basal levels of IL-6 in patients with IBS (10,19).

Dinan et al. investigated the time response (up to 180 minutes) to the ingestion of pyridostigmine, an acetylcholinesterase inhibitor, and observed a significant time interaction for IL-6 in patients with IBS compared to the CG and a set of patients with depression, which was not found for IL-9 or IL-10. Moreover, levels of IL-6 at 60 and 90 minutes following the administration of the drug were significantly correlated with the symptom score in patients with IBS. Prior administration of procyclidine, an antimuscarinic, to pyridostigmine attenuated this response in IL-6 levels in patients with IBS, as well as the exacerbation of the symptoms observed at 60 and 90 minutes. All the patients exhibited an exacerbation of the symptoms following the administration of pyridostigmine, which did not occur if procyclidine was administered previously (17).

Liebregts et al. (15) observed higher levels of stimulated TNF-α in subsets of patients with D-IBS and PI-IBS; higher levels of stimulated IL-6 in patients with IBS, and in subsets with D-IBS and PI-IBS; and higher levels of stimulated IL-1β in patients with D-IBS, C-IBS and A-IBS. On the other hand, levels of stimulated TNF-α were regular in patients with IBS and C-IBS; levels of stimulated IL-1β were also normal in patients with IBS and levels of stimulated IL-6 were normal in patients with C-IBS.

On the contrary, Öhman et al. (20) observed an increase in the secretion of stimulated IL-1β in peripheral blood mononuclear cells, without encountering differences between the different subsets of patients with IBS. Moreover, higher levels of stimulated TNF-α, IL-6 and IL-1β were found in patients that had more than three bowel movements per day, pain associated with diarrhoea, urgency or watery stools compared with patients without these symptoms or with constipation (15).

A decrease in basal levels of IL-10 and in the ratio of IL-10/IL-12 was discovered as well as an increase in IL-12 levels which restored to following the administration of the probiotic Bifidobacterium infantis, which did not occur with the administration of the probiotic Lactobacillus salivarius (4). Other authors, on the other hand, observed regular basal levels of IL-10 in patients with IBS (13,17,19) and D-IBS (14).

The β-adrenergic modulation of IL-10 and TNF-α is regular in patients with D-IBS (increase of the first and inhibition of the second). The decrease in TNF-α modulated by glucocorticoids was also normal, which indicates that patients with D-IBS show normal sensitivity to corticoids (14).

One study (19) found an increase in the production of IL-5 and IL-13, and a reduction in the production of IL-10 (though not significant, p=0.06) in peripheral blood mononuclear cells. However, another study observed regular stimulated IL-10 levels.

Finally, a number of studies presented normal levels of IFN-γ and IL-2 secretion in patients with IBS, without encountering differences between the various patient subsets (6,20).

Cytokines in the intestine

Up to 33 genes were found, each with a different expression, in the sigmoid colon mucosa in patients with IBS (16).

In these patients, a lower secretion of IL-8 and regular levels of IL-1β, TNF-α and IL-6 were described in the sigmoid colon (16). Other studies find diminished levels of IL-2 and Il-6 mRNA, and regular expression levels of IL-1, IL-10, IL-12, the IL-10/IL-12 ratio, IFN-δ, TNF-α in the sigmoid colon of patients with IBS. The pattern of reduced cytokine expression in the colon encountered in these patients has not been described thus far for any other pathology (16,18).

Abnormal levels of IL-1, IL-2, IL-6, IL-10, IL-12, IL-10/IL-12, IFN-δ and TNF-α mRNA expression in the rectum of patients with IBS have not been found (18).

In a group of patients with gastroenteritis, the IL-1β mRNA expression in the rectal mucosa was higher in the group of patients which subsequently developed PI-IBS than in those patients which did not develop it (7). Furthermore, a higher expression of IL-1β mRNA was found in the terminal ileum and rectosigmoid mucosa in patients with PI-IBS compared with patients with non-PI-IBS and the CG (9). Similarly, Khan et al. (5) also observed a higher expression of IL-1β mRNA in the colon mucosa of patients with D-IBS.

Finally, IFN-γ levels in the ascending colon of patients with IBS appear to be high, though not significantly (12).

O'Mahony et al. postulate that the disorder responds to a Th1-type cytokine profile (4,16), while Kindt et al. are of the opinion that a change in cytokine production from Th1 to Th2 takes place (19).

CONCLUSIONS OF THE AUTHORS

It cannot be affirmed whether a clear trend in the cytokine profile presented by patients with IBS exists given that the findings in their levels differ between the various studies. This may be due to the methodology of analysis employed and/or the diagnosis criteria used, even though the majority of the studies made use of the Rome II Criteria.

However, a trend appears to exist as regards the presence of high levels of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8) and diminished levels of the anti-inflammatory cytokine IL-10.

The persistence of "low-grade intestinal inflammation" in patients with IBS may be the result of a higher ratio or percentage of pro-inflammatory cytokines and/or lower ratio or percentage of anti-inflammatory cytokines, giving rise to an imbalance in the activity of said cytokines.

It is postulated that there may be a dysfunction in the down-regulation of the pro-inflammatory response subsequent to the emergence of a triggering factor thereof (an gastrointestinal infection, for instance), which would maintain the IBS condition.

The alteration of the cytokine level has been associated with changes brought about in the hypothalamic-pituitary-adrenal (HPA) axis: altered serum cytokine levels in patients with IBS seem to be associated with a highly active HPA axis.

IL-6 appears to play an important role in the generation of the symptoms and a connection has been found between this and the HPA axis, which has not been discovered for IL-8. However, it is unknown whether this is the result of the alteration centrally, peripherally or at both levels. The alteration of blood cytokine levels could also account for the non-gastrointestinal (psychological) symptoms that appear in these patients.

Moreover, there are indications that give reason to believe that the different subgroups of patients with IBS could present a cytokine profile in different blood. Nevertheless, the small sample sizes used in the studies and the disparity of the findings render it difficult to uphold this assertion. Further studies are called for with regard to the role of TNF-α, IL-1β and IL-6 in the subgroup of patients with diarrhoea-predominant IBS and PI-IBS, given that it appears that they can be increased in these patient subgroups.

As far as the intestine is concerned, contrary to what would be expected on account of the higher presence of immune cells (see part one of this review), high gene expression levels of cytokines have not been detected (but rather diminished levels) nor have high cytokine secretion levels been observed, which gives reason to believe an effective inflammatory response in the tissue is not being triggered. The decrease in the gene expression of some cytokines does, however, point to the existence of an imbalance at this level in the intestine of patients with IBS.

The role of mast cells in IBS, of which there is a high concentration adhered to nerve endings in the intestinal mucosa, could be associated with an interaction with the nervous system rather than with the release of cytokines in the intestine.

In two studies high levels of IL-1β expression were found in patients with PI-IBS, which leads us to believe that the underlying inflammation could contribute to the emergence and persistence of IBS in patients who have previously had an episode of acute infectious gastroenteritis.

Sufficient data does not exist in order to uphold the existence of a Th1- or Th2-type profile in these patients. Nevertheless, the indications invite us to continue delving deeper into the study of this phenomenon.

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